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Practical Synthesis of α,β-Alkynyl Ketones by Oxidative Alkynylation of Aldehydes with Hypervalent Alkynyliodine Reagents

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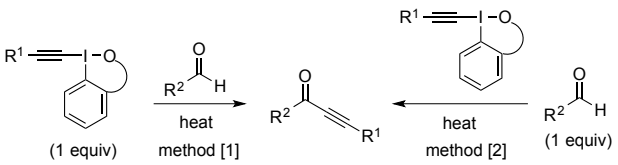
A practical, metal-free carbonyl C(sp^2)–H oxidative alkynylation of aldehydes with hypervalent alkynyliodine reagents without the use of any catalysts is described for the synthesis of various α,β-alkynyl ketones. Here, two different methods have been developed where limiting reagents or substrates can be switched each other, and adopted them according to the valuableness of aldehyde substrates or hypervalent alkynyliodine reagents. These reactions proceed with a broad substrate scope and high functional-group compatibility.

Keywords: Alkynyl ketone, Hypervalent alkynyliodine reagent, Metal-free

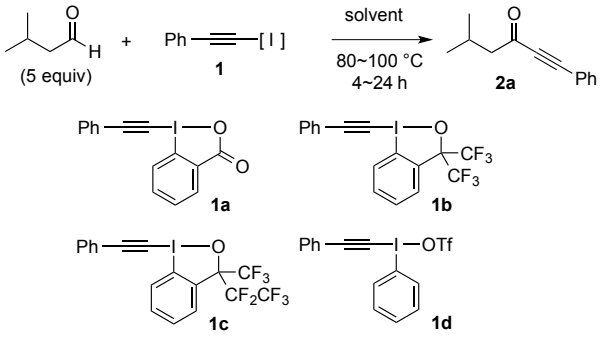
α,β-Alkynyl ketones are important structural units in various bioactive molecules and materials.[1,2] Accordingly, there are numerous approaches so far for the synthesis of such α,β-alkynyl ketones.[3] Classical and traditional approaches have involved the direct nucleophilic addition of alkynyl anions to carbonyl derivatives.[1c,2a,2b,2d,4] More recently, some radical approaches involving oxidative alkynylation of aldehydes with hypervalent 1-alkynyl-1,2-benziodoxol-3(1H)-one under the influence of stoichiometric *tert*-butyl hydroperoxide or photoredox catalysis.[5-7] In this context, we are interested in the possibility of developing a practical and atom-economical approach to α,β-alkynyl ketones based on the oxidative alkynylation of aldehydes with hypervalent alkynyliodine reagents without the use of any other reagents or catalysts. Here we wish to report our initial study on this subject, in which we developed two different methods, based on the use of either 1 equiv of aldehyde substrate or 1 equiv of alkynyliodine reagents (Scheme 1). These two methods would be complementary and necessary, if either alkynyliodine reagent or aldehyde substrate would be very valuable.



Scheme 1. Two different approaches for the synthesis of α,β-alkynyl ketones.

Initially, reaction of excess 3-methylbutanal (5 equiv) with 1 equiv of 1-[phenylethynyl]-1,2-benziodoxol-3(1H)-one (**1a**) was carried out in benzene at 80 °C for 4 h to furnish 5-methyl-1-phenylhex-1-yn-3-one (**2a**) in 23% yield (entry 1). In contrast, switching a hypervalent iodine reagent from **1a** to bis(trifluoromethyl) derivative **1b** under otherwise similar heating condition afforded **2a** in much better yield (entry 2). Use of 3 or 1.2 equiv of aldehydes lowered the yields of **2a** (entry 3). The solvent effect is found to be very critical (entries 2 and 4-8). Though THF and DMF as solvent are not acceptable for this transformation (entries 4 and 5), MeCN and DCE afforded higher yields of **2a** (entries 7 and 8). The reaction temperature and time are somewhat important, and the use of 80 °C for 12 h gave the highest yield of **2a** (entry 9). The reaction proceeded smoothly without irradiation of light (entry 10). Again, the use of **1a** under similar reaction condition resulted in much lower yield (entry 11). Switching to other hypervalent alkynyliodine reagents **1c** and **1d** lowered the chemical yields (entries 12 and 13). Use of longer reaction time, higher or lower temperature, and higher concentration (1.0 M vs. 0.5 M) of the solution gave rise to the inferior results (entries 14~17).

Table 1. Optimization of the oxidative alkynylation of aldehydes with hypervalent iodine reagent[a]



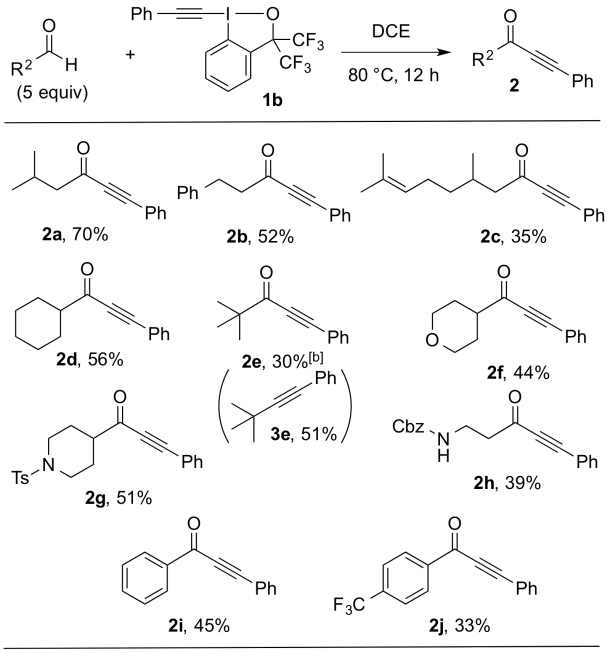
Entry	Reagent	Solvent	Condition (°C, h)	Yield (%)[b]
1	**1a**	benzene	80, 4	23
2	**1b**	benzene	80, 4	51
3	**1b**	benzene	80, 4	49,[c] 39[d]
4	**1b**	THF	80, 4	12
5	**1b**	DMF	80, 4	34
6	**1b**	PhCl	80, 4	57
7	**1b**	MeCN	80, 4	67
8	**1b**	DCE	80, 4	68
9	**1b**	DCE	80, 12	72 (70)

10	**1b**	DCE	80, 12	69[e]
11	**1a**	DCE	80, 12	48
12	**1c**	DCE	80, 12	33
13	**1d**	DCE	80, 12	4
14	**1b**	DCE	80, 24	63
15	**1b**	DCE	50, 24	57
16	**1b**	DCE	100, 12	59
17	**1b**	DCE	80, 12	57[f]

[a]Reaction conditions unless otherwise noted: 3-methylbutanal (1 mmol), reagent **1** (0.2 mmol) in solvent (0.5 M) under indicated condition. [b]The yield was determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. Isolated yield is given in parentheses. [c]Use of 3 equiv of aldehyde. [d]Use of 1.2 equiv of aldehyde. [e]Under dark atmosphere. [f]Use of 1.0 M solution.

With the optimized conditions in hand, we subsequently examined the scope of the oxidative alkynylation with **1b** with respect to various aldehyde substrates (**2**) as shown in Table 2. Not only *prim*-alkyl substituted aldehydes but also *sec*- and *tert*-alkyl substituted aldehydes are employable. In case of pivalaldehyde under the standard condition (80 °C, 12 h), decarbonylation took place before the C–C bond formation, thereby giving *tert*-butyl phenyl acetylene (**3e**) in 51% yield.[6b,8] Fortunately, the similar reaction at 50 °C could totally suppress the undesired decarbonylation to furnish the desired **2e** in moderate yield. In addition, heterocyclic aldehydes and aromatic aldehydes afforded the corresponding alkynylation products in good yields. In case of benzaldehyde, **2i** was obtained with 41% recovery of **1b** by NMR analysis.

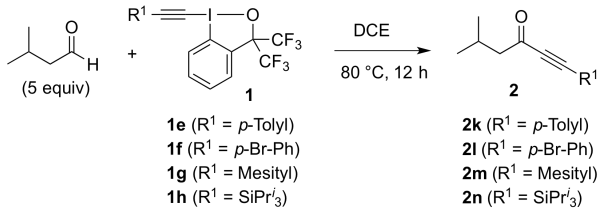
Table 2. Substrate scope[a]



[a]Reaction conditions unless otherwise noted: aldehyde (1.0 mmol), reagent **1b** (0.2 mmol) in solvent (0.5 M) under indicated condition. [b]At 50 °C for 24 h.

The scope of the oxidative alkynylation with respect to alkynyliodine reagents (**1**) is summarized in Table 3. *para*-Tolyl-, *para*-bromophenyl- and mesitylalkynyliodine reagents **1e~g** as well as triisopropyisilylalkynyliodine reagent **1h** can be successfully utilized for the oxidative alkynylation of 3-methylbutanal. However, attempted reaction of cyclohexanecarbaldehyde with ethynyliodine reagent 1 (R^1 = H) was unsuccessful.

Table 3. Scope of alkynylation reagents[a]

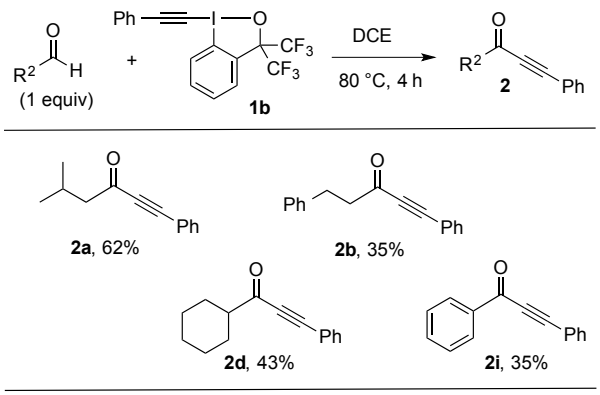


Entry	Reagent 1	Product 2	Yield (%)
1	**1e**	**2k**	62
2	**1f**	**2l**	54
3[b]	**1g**	**2m**	63
4	**1h**	**2n**	51

[a]Reaction conditions unless otherwise noted: 3-methylbutanal (1.0 mmol), reagent **1** (0.2 mmol) in solvent (0.5 M) under indicated condition. [b]Reaction was conducted in 0.1 mmol scale.

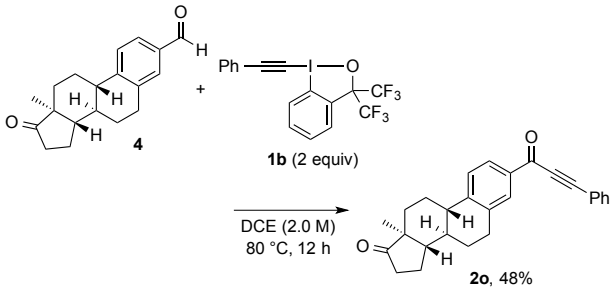
Although aldehyde substrates are generally abundant and readily available, the use of excess amount of substrates would be inconvenient in certain case such as the late-stage functionalization of complex molecules. Thus, we also developed the other method, based on the use of 1 equiv of aldehyde substrate under otherwise similar reaction conditions. Indeed, the reaction of 3-methylbutanal (1 equiv) with 1.2 equiv of **1b** was carried out in DCE (2.5 M) at 80 °C for 4 h to furnish 5-methyl-1-phenylhex-1-yn-3-one (**2a**) in 62% yield. Use of excess **1b** (2 equiv) did not affect the yield. It should be noted that the use of a 2.5 M solution is found to be crucial, and attempted use of a more dilute solution (0.5 M) lowered the yield (39%) of **2a**. With this reaction condition at hand, several different aldehydes are susceptible to the oxidative alkynylation with **1b** (1.2 equiv) as shown in Table 4 (See also the Supporting Information).

Table 4. Substrate scope[a]



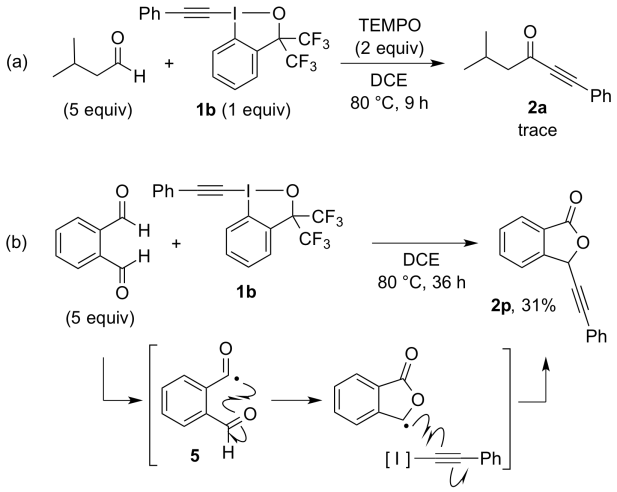
[a]Reaction conditions unless otherwise noted: aldehyde (0.2 mmol), reagent **1b** (0.24 mmol) in solvent (2.5 M) under indicated condition.

Furthermore, the synthetic utility of this approach was demonstrated by the reaction of hypervalent alkynyliodine reagent **1b** with estrone-derived substrate **4**, affording the desired product **2o** in 48% yield (Scheme 2). This result indicates that our method is potentially applicable to the late-stage functionalization in the total synthesis of bioactive molecules.



Scheme 2. Synthetic application using estrone derivative **4**.

In order to elucidate the reaction mechanism, we carried out several control experiments. When the reaction of 3-methylbutanal (5 equiv) with 1 equiv of **1b** was executed in DCE at 80 °C for 9 h in the presence of a radical scavenger, 2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO), the alkynylation was totally inhibited, and **1b** was recovered in >90% yield (Scheme 3a). This result implies some radical intermediates are most likely participated in this alkynylation. In addition, a solution of *o*-phthalaldehyde (5 equiv) in DCE was treated with 1 equiv of **1b** at 80 °C to furnish cyclization product **2p**, implying the intervention of acyl radical intermediate **5** (Scheme 3b). We assume that the coordination of aldehyde carbonyl to electrophilic iodine(III) reagent **1b** might accelerate the acyl radical formation with trace amounts of oxygen gas in a reaction system.



Scheme 3. Control experiments with (a) TEMPO and (b) *o*-phthalaldehyde.

In conclusion, we have developed two different ways of preparing various α,β-alkynyl ketones from aldehydes with hypervalent alkynyliodine reagents in the absence of any catalysts under mild, metal-free conditions. These methods can be properly used depending on the valuableness of aldehyde substrates and alkynyliodine reagents. The generality of these approaches was well demonstrated with various types of aldehydes, including aliphatic (*prim*-, *sec*-, and *tert*-alkyl) aldehydes and aromatic aldehydes. Further investigations into the applications of such a practical, metal-free oxidative alkynylation strategy for various aldehydes for the physiologically active compounds are currently in progress in our laboratory.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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